Bioequivalence Study of 75 mg Venlafaxine Hydrochloride Extended Release Capsules in Healthy Thai Volunteers

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ABSTRACT

Objective: The purpose of this study is to determine the bioequivalence of a 75 mg dose of venlafaxine hydrochloride extended release capsule formulations between the test product (Valosine® S.R., Standard Chem. & Pharm. Co., Ltd., Taiwan) and the reference product (Efexor®-XR, Wyeth-Ayerst Ireland Co., Ltd).

Methods: An open-labeled, multiple-dose with food, 2-treatment, 2-period, 2-sequence, randomized crossover study was conducted in 24 healthy Thai volunteers. Each volunteer received a 75 mg capsule of the reference or test drugs for 6 consecutive days. On the 6th day of dosing, blood samples were collected before dosing at various time points up to 24 hours after dosing and on the other days (the 1st, 4th and 5th day of dosing) pre-dose blood samples were also collected for steady state confirmation. Analysis of venlafaxine concentrations was performed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The pharmacokinetic parameters including $C_{\text{ss}}$, $AUC_{0-24(h)}$, $T_{\text{ssmax}}$ and $t_{1/2}$ were analyzed using the non-compartmental model. Drug safety and tolerability were assessed.

Results: Twenty-three volunteers completed both treatment periods. The geometric mean ratios (Test/Reference) between the two products of extended-release venlafaxine capsule were 88.80% (81.46%-96.80%) for $C_{\text{ssmax}}$ ratios and 101.10% (95.02%-107.56%) for $AUC_{0-24(h)}$ ratios. There was no significant difference of the $T_{\text{ssmax}}$ parameter between the two formulations ($p > 0.05$). No serious adverse events related to the study drugs were found.

Conclusion: The two products of venlafaxine hydrochloride extended release capsules are bioequivalent. Both products are well tolerated.

Keywords: Bioequivalence, venlafaxine

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Depression and anxiety are two of the most important problems in psychiatry. They are of high prevalence and major world-wide public health problems. Venlafaxine is the first of a new class of antidepressants or atypical antidepressants that selectively inhibits the neuronal uptake pumps for both serotonin and noradrenaline (SNaR). Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake. It has no significant affinity for muscarinic cholinergic, H1-histaminergic, or $\alpha_1$-adrenergic receptors in vitro. Whereas it has similar efficacy when compared with classical antidepressants, it has better-tolerated adverse effects and is less likely to produce high cardiac toxicity of tricyclic antidepressant drugs and drug-drug interactions of nonselective monoamine oxidase inhibitors (MAOIs). Venlafaxine hydrochloride is a structurally novel antidepressant. It is designated as $(R/S)$-1-[(2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride or $(\pm)$-1-[(dimethylamino) methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2\cdot HCi$ and a molecular weight of 313.87.

Steady-state concentrations of venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), in plasma are attained within 3 days of oral multiple dose
therapy. The extended release venlafaxine capsule, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet. The observed mean (SD) apparent steady-state volume of distribution of 7.5 (3.7) and 5.7 (1.8) L/kg for venlafaxine and ODV, respectively, has been reported. Metabolism of venlafaxine occurs primarily via CYP2D6 and CYP3A4 (cytochrome P-450 isozyme). Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 to 450 mg/day. It has been shown that the mean (SD) values of steady-state plasma clearance of venlafaxine and ODV are 1.3 (0.6) and 0.4 (0.2) L/h/kg, respectively and the clearance decreases with cirrhosis, renal impairment and dialysis. Apparent elimination half-lives of venlafaxine and ODV are 5 ± 2 and 11 ± 2 hours, respectively. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

The bioequivalence study of two formulations of 75 mg venlafaxine hydrochloride extended release capsule formulations was examined between generic drug Valosine® S.R. (Standard Chem. & Pharm. Co., Ltd., Taiwan) as the test product and Efexor®-XR from Wyeth-Ayerst Ireland Co., Ltd as the reference product. This bioequivalence study could give assurance when prescribing less expensive generic drugs as alternatives with similar efficacy and safety.

MATERIALS AND METHODS

Study drugs
Valosine® S.R. provided by Standard Chem. & Pharm. Co., Ltd. (Taiwan) and Efexor®-XR from Wyeth-Ayerst Ireland Co., Ltd. were used as the test and the reference products, respectively. Both products were prepared as venlafaxine hydrochloride equivalent to venlafaxine 75 mg.

Study population
The study was carried out at the Siriraj Clinical Research Center, Siriraj Hospital, Bangkok, Thailand. The study protocol was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand and the Thai Food and Drug Administration, Ministry of Public Health, Thailand.

In addition, the protocol was performed in accordance with the Declaration of Helsinki Principles as outlined in the Guidelines for Good Clinical Practice (GCP). All subjects were given a detailed description of the study and written informed consent was obtained prior to the enrollment. Twenty-four healthy male and female volunteers between the ages of 18-45 years with a body mass index between 18-24 kg/m² were assessed to be in good physical condition by a complete medical screening including a medical history, physical examination and laboratory screening test for hematologic and blood biochemistry parameters. Female volunteers who were pregnant or lactating were not eligible for participation. Subjects with a history of hypersensitivity to any ingredients in the venlafaxine products and/or related drugs or its constituents or who were taking any medication or alcohol for a 14-day period prior to the study were excluded. Subjects who had a history of cardiovascular, hepatic, renal, gastrointestinal or hematologic disease were excluded from the study.

Study design
The study was an open-labeled, multiple-dose study taken with food, two-treatment, two-period, two-sequence randomized crossover with at least one week washout period. Subjects were randomly allocated to two groups by the sequence of product administered [Test-Reference (TR) and Reference-Test (RT) group]. In each period, one 75 mg capsule of venlafaxine hydrochloride of the test or reference product was administered 30 minutes after starting a standard breakfast at the same time in the morning for 6 consecutive days. Subjects were required to visit the research clinic 5 consecutive days for study of drug dosing and were hospitalized at the research ward on the 6th day of dosing for 24 hour blood sampling. After a minimum of 1 week washout period, the subjects were crossed-over to the next treatment following the same procedure as conducted in the 1st period.

Sample collection
During hospitalization on the 6th day of dosing, blood samples of 6 mL each (vacuum heparinized tubes) were drawn from the venipuncture prior to drug administration (0 h) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours after dosing.

On the 1st, 4th and 5th day of dosing, pre-dose blood samples of the same amount were drawn directly from a vein for steady state confirmation. Serum was separated by centrifugation and then stored at -70°C until analysis.

Venlafaxine analysis by LC-MS/MS
Briefly, 25 microliters of paroxetine hydrochloride as an internal standard (IS) solution was added to serum sample or venlafaxine standard serum. After being well mixed, all samples were added with aqueous ammonia to adjust to an alkaline pH. The organic layer was transferred into a new conical polypropylene tube and evaporated under a nitrogen stream until the sample was dried. The residue was reconstituted with 100 µL of a reconstituting solvent and 20 µL of the reconstituted residue was injected into the LC-MS/MS system.

The mass spectra were obtained using a Quattro Micro mass spectrometer (Micromass, UK) equipped with an electrospray ionisation source. The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode. Sample introduction and ionization was electrospray ionization in the positive ion mode. The mass transition ion-pair was selected as m/z 278.18 > 121.14 and 278.18 > 147.07 for venlafaxine hydrochloride and as m/z 330.04 > 69.99 for paroxetine hydrochloride. The data acquisition was ascertained by Masslynx 4.0 software. Validation of this method was performed as recommended by USFDA.

Pharmacokinetic and statistical analysis
For the purpose of bioequivalence analysis, (AUC(0-t)) ss and Cmax were considered as the primary variables. Two-way analysis of variance (ANOVA) for crossover design was performed for log-transformed data and used to assess the effect of formulations,
Bioanalysis and pharmacokinetics

Serum venlafaxine was measured by the LC-MS/MS method. The calibration curves were found to be linear over the concentration range of 0.5-300.0 ng/mL for venlafaxine hydrochloride. The coefficient of determination ($r^2$) was 0.998745. The between-run precision (CV) was 7.09%-5.498%. The average % recoveries of the within-run and between-run accuracy were 93.883%-104.720% and 98.175%-100.423%, respectively.

No significant difference was observed in any of the analyzed pharmacokinetic parameters (Table 2). $AUC_{0-24(ss)}$ for the reference and test formulations was 1,780 ng.h/mL and 1,790 ng.h/mL, respectively whereas $C_{ss}^{max}$ and $T_{ss}^{max}$ for the reference and test formulations were 121.0 ng/mL, 5.17 h and 110.0 h/mL, 5.78 h respectively.

Bioequivalence analysis

Ninety percent confidence interval of geometric mean ratios of bioavailability parameters between the test and reference formulation are presented in Table 3. The statistical analysis obtained from this study showed that the point estimate (90% CI) of the geometric mean ratio (T/R) of $C_{ss}^{max}$ and $AUC_{0-24(ss)}$ was entirely within the equivalence criteria (80.00-125.00%) which was 88.80% (81.46%-96.80%) for $C_{ss}^{max}$ ratios and 101.10% (95.02%-107.56%) for $AUC_{0-24(ss)}$ ratios. In addition, no significant difference of the $T_{ss}^{max}$ parameter between the two studied formulations was observed ($p >0.05$). Therefore, it was concluded that the two extended-release capsule formulations of venlafaxine were bioequivalent in terms of rate and extent of absorption.

Tolerability

Almost all volunteers taking both venlafaxine formulations were noted for mild adverse events. Most common events were drowsiness, nausea and loss of appetite. However, no subject had any severe adverse event or withdrew from the study because of an adverse event.

DISCUSSION

In Thailand, a number of patients suffer from depression which can cause a problem in quality of

TABLE 1. Demographic data and baseline characteristics of volunteers.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (TR Group)</th>
<th>Group 2 (RT Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=12)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 6</td>
<td>Male: 6</td>
</tr>
<tr>
<td></td>
<td>Female: 6</td>
<td>Female: 6</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>26.1 ± 6.6</td>
<td>26.3 ± 4.6</td>
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<tr>
<td>Weight (kg ± SD)</td>
<td>60.0 ± 10.7</td>
<td>59.4 ± 9.6</td>
</tr>
<tr>
<td>Height (cm ± SD)</td>
<td>166.8 ± 9.5</td>
<td>167.6 ± 5.1</td>
</tr>
<tr>
<td>Body mass index (kg/m² ± SD)</td>
<td>21.4 ± 2.1</td>
<td>21.1 ± 2.3</td>
</tr>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C ± SD)</td>
<td>36.8 ± 0.2</td>
<td>36.7 ± 0.1</td>
</tr>
<tr>
<td>Pulse (beats/minute ± SD)</td>
<td>72.0 ± 9.8</td>
<td>76.4 ± 6.9</td>
</tr>
<tr>
<td>Respiratory rate (times/minute ± SD)</td>
<td>19.9 ± 0.7</td>
<td>20.0 ± 0.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg ± SD)</td>
<td>110.4 ± 8.7</td>
<td>110.8 ± 10.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg ± SD)</td>
<td>72.3 ± 9.1</td>
<td>73.0 ± 7.4</td>
</tr>
</tbody>
</table>

$T_{ss}^{max}$ = The time to peak at steady state, $T_{1/2}$ = Serum concentration half-life, $AUC = $ Area under the concentration-time curve, $C_{ss}^{max}$ = The maximum serum drug concentration at steady state

demonstrates the demographic characteristics, which were not statistically different between groups.

**RESULTS**

Study population

Twenty four healthy Thai adults eligible for the study enrollment were randomly divided into 2 groups [Test-Reference (TR) and Reference-Test (RT)] according to the sequence of drug administration. However, one volunteer withdrew from the study due to personal reasons in the first period. Consequently, the TR and RT group consisted of twelve and eleven subjects, respectively. Thus this study was unbalanced in each sequence and the results from 23 volunteers were used for pharmacokinetic and statistical analysis. Table 1 demonstrates the demographic characteristics, which were not statistically different between groups.
their lives and families. Venlafaxine, a selective SNRI has similar efficacy and better tolerability when compared to classical antidepressants.

An open-labeled, multiple-dose with food, two-treatment, two-period, two-sequence randomized crossover design in 24 healthy volunteers was considered appropriate and standard for bioequivalence evaluation of the generic and the reference products. The multiple-dose, steady-state study simulates real life conditions including the influence of meals as well as circadian effects on the performance of the extended release product. For a safety reason, co-administration of the drug with food can reduce nausea, a common side effect of venlafaxine.

In general, the pharmacokinetic parameters for both formulations were similar to the pharmacokinetic parameters of venlafaxine in previous published data.\(^2,3,7\) This study demonstrated that 90% CI of the logarithmic transformed of steady state parameters \(C_{\text{ss max}}\) and \(AUC_{0-24}(\text{ss})\) were contained in 80.00-125.00%. In addition, no significant differences of the \(T_{\text{ss max}}\) values between the two formulations were observed \((p >0.05)\). Therefore, the two extended-release capsule formulations of venlafaxine are considered bioequivalent in terms of the rate and extent of absorption. Moreover, both formulations were well tolerated.

In conclusion, the test (Valosine® S.R.) and reference (Efexor® XR) products of venlafaxine 75 mg are bioequivalent.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


**TABLE 3.** Statistical summary of the comparative bioavailability data \((n=23)\).

<table>
<thead>
<tr>
<th>Dependent</th>
<th>Geometric mean ratio (T/R)</th>
<th>90% Lower limit</th>
<th>90% Upper limit</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln (\left(C_{\text{ss max}}\right))</td>
<td>88.80</td>
<td>81.46</td>
<td>96.80</td>
<td>0.9938</td>
</tr>
<tr>
<td>Ln (\left(AUC_{0-24}(\text{ss})\right))</td>
<td>101.10</td>
<td>95.02</td>
<td>107.56</td>
<td>0.9999</td>
</tr>
</tbody>
</table>

T = Test product  R = Reference product

![Fig 1. Geometric mean of serum concentration-time profile of venlafaxine \((n=23)\); Normal plot (above) and semilog plot (below).](image-url)